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Association of Prenatal Vascular Disruptions With Decreased Maternal Age

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Disruptions of fetal structures can create a variety of congenital anomalies. Some apparent prenatal vascular disruptions associate strongly with decreased maternal age, and are rare with older mothers. This is well-documented for gastroschisis, but similar findings with hydranencephaly suggest a general phenomenon that may also involve porencephaly, septo-optic dysplasia, early body stalk disruptions, certain hemifacial anomalies, and other findings. Prenatal vascular disruption may be a common cause of congenital anomalies, but its nature is unknown, and obvious environmental confounders associated with decreased maternal age may have only relatively small contributions. A protective effect for pregnancies of older mothers also remains a possibility. Am. J. Med. Genet. 69:237–239, 1997.

KEY WORDS: gastroschisis; hydranencephaly; maternal age; septo-optic dysplasia; vascular disruption

INTRODUCTION

Prenatal vascular events can disrupt fetal structures, creating a variety of congenital anomalies [Van Allen, 1981]. Gastroschisis, one such apparent finding, shows a distinct epidemiology with a strong association with decreased maternal age (DMA) and a paucity of older mothers. Hydranencephaly, another such finding, shows a similar effect, and analysis of septo-optic dysplasia suggests a general phenomenon of unknown cause. Other anomalies of this sort may also be involved, although exceptions do exist. This may be a relatively common cause of a variety of congenital anomalies.

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EVIDENCE FOR AN ASSOCIATION OF DMA WITH PRENATAL VASCULAR DISRUPTIONS

Gastroschisis, a ventral body wall defect, is a probable vascular disruption. It is the easiest of such anomalies to study in terms of frequency, ease of diagnosis, and clinical homogeneity. Multiple studies have shown a distinct epidemiology with a clear DMA effect and a paucity of older mothers [Curry et al., 1993].

For institutionalized patients with hydranencephaly, a vascular disruption of the brain [Friede, 1989; Hunter, 1993], 10/16 mothers were teenaged, significantly more than population and institutional controls. Only 1 mother was over 29 years old [Lubinsky et al., 1997]. In a population study, teenage mothers had an almost 10-fold greater risk than mothers over age 30 years [Lubinsky and Torfs, 1996].

Increased illegitimacy with hydranencephaly [Opitz et al., 1982; Friede, 1989; Lubinsky et al., 1997] may be secondary to a high rate of out-of-wedlock births to younger mothers.

Increased illegitimacy was also seen with porencephaly [Dekaban, 1965], which can be part of the same spectrum of brain vascular disruptions as hydranencephaly [Friede, 1989].

Younger mothers predominate with septo-optic dysplasia [Lippe et al., 1979]. This variable combination of septum pellucidum, optic nerve, and pituitary anomalies is almost always sporadic. It associates with porencephaly, a vascular anomaly, and makes little embryologic sense. Components develop at different times and arise from different tissues and processes. Vascular disruptions, perhaps involving the proximal trunk of the anterior cerebral artery, are more likely than a dysplasia or some other classical developmental process [Lubinsky, 1997].

DISCUSSION

Gastroschisis, hydranencephaly, and septo-optic dysplasia all have significant excesses of younger mothers. The magnitude of this effect, plus a relative rarity of older mothers for at least the first two conditions [Curry et al., 1993; Lubinsky et al., 1997; Lubinsky and Torfs, 1996], differs greatly from patterns seen with most other congenital anomalies [Croen and Shaw, 1995], and suggests a common pathogenesis.

While alternatives have been proposed for vascular disruptive involvement with gastroschisis and septo-optic dysplasia, there are strong arguments for this process [Curry et al., 1993; Lubinsky, 1997]. However, there is little question for hydranencephaly [Hunter, 1993], and the distinct DMA epidemiology suggests a common link that is obscure with other proposed origins.

DMA effects can be complex. Even genetic traits can be affected (e.g., polydactyly and piebaldism in guinea pigs [Wright, 1926]), and the nature of the suggested phenomenon is unclear. It also should be noted that, despite a focus on risk factors at lower ages, a protective effect for older mothers could give a similar epidemiology even with a diverse set of causes.

Vascular disruptions are, indeed, diverse: diabetes, prenatal infections, embolization or coagulopathy from a deceased twin, including fetal papyraceus, twin-twin transfusions, and anatomic variants of the umbilical cord have all been implicated [Benirschke and Kaufmann, 1990; Hoyme et al., 1982], and clearly vascular findings can also be part of chromosomal or genetic syndromes at times (e.g., cutis aplasia [Manino et al., 1977; Der Kaloustian, 1993]).

However, most such etiologies should not show a DMA effect, and a paucity of older mothers suggests a single age-sensitive effect for most cases of gastroschisis and hydranencephaly. This may reflect at least relative causal homogeneity for these conditions, which are mostly sporadic, and rare with aneuploidy, Mendelian disorders, and nondisruption anomalies. Still, this is probably not absolute, and gastroschisis with multiple vascular anomalies does not appear to be age-related [Calzolari et al., 1995; Yang et al., 1992].

Greater heterogeneity of other disruption anomalies may obscure DMA effects, but possibilities exist with other cases. For body stalk agenesis and amelia with other gross body wall defects, all possible vascular disruptions [Luebke et al., 1990; Mastroiacovo et al., 1992] found a high rate of young mothers. Also, for cutis aplasia, Cockayne [1933] noted a tendency for affected children to be firstborn.

Hemifacial findings may also have vascular origins [Poswillo, 1973; Robinson et al., 1990]. In a California clinic, I found an average maternal age 3 years lower for isolated cases than cleft lip ± palate controls, and no mothers over age 29 years. Numbers were small (12) but results were suggestive ($P = 0.065$). Such analyses may help distinguish cases with a "standard" vascular disruptive etiology from those with other origins, such as hemifacial anomalies with epibulbar dermoids, which are difficult to see as vascular findings.

However, a DMA effect was absent with limb defects [Mastroiacovo and Botto, 1994] that are probably of vascular origin [Bavinck and Weaver, 1986]. Interestingly, this is the only vascular finding noted with chorionic villus sampling (cvs), which is often done for advanced maternal age [Mastroiacovo and Botto, 1994]. If this is a unique exception, then other disruptions might be potentiated with cvs at younger ages, giving anomalies not seen in current studies.

Confounding factors are possible, but unclear [Drongowski et al., 1991; Goldbaum et al., 1990; Haddow et al., 1993; Torfs et al., 1994; Werler et al., 1992a,b]. Low parity is not the answer alone [Hemmunki et al., 1982]. High illegitimacy with por- and hydranencephaly [Opitz et al., 1982; Dekaban, 1965; Friede, 1989] may only be secondary [Lubinsky et al., 1997], but events such as attempted terminations are possible [Warkany et al., 1981]. Influences may also have changed: all cited illegitimate births were before 1985 and, despite some increases in gastroschisis rates [Curry et al., 1993], no epidemic of disruptions has been noted since [Martin et al., 1992], despite rising teenage illegitimacy [Guhleman, 1993].

Younger mothers also tend to have a lower socioeconomic status, but a dearth of older mothers with gastroschisis and hydranencephaly is hard to explain on this basis. Also, despite a higher rate of younger mothers and a generally lower socioeconomic status, gastroschisis is relatively rare, and a DMA effect smaller, in blacks than in whites [Center for Disease Control, 1993; Yang et al., 1992; Lubinsky et al., 1995].

Cocaine, with its vascular effects, might have a role, but pregnant users tend to be slightly older than other childbearing women, and greater use by blacks [Robins and Mills, 1993] is not reflected in racial incidences of gastroschisis [Center for Disease Control, 1993; Lubinsky et al., 1995; Yang et al., 1992]. Also, DMA observations in gastroschisis predate current drug use patterns, and no epidemic of disruptions has been noted recently [Martin et al., 1992], making a primary role unlikely. The DMA effect also suggests caution in studying cocaine teratogenesis: if vascular pathogeneses are being considered, then incidence rates should be from children of age-controlled mothers, and not from general population figures.

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